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Description

This invention r lates generally to a novel sustained-release formulation which gradually releases a m dicinal agent therefrom. Specific embodiments of the invention ar formulations for slowly disp nsing a drug in the eye.

It is basically known in the art that medicinally active substances may be dissolved in the aqueous constituent of hydrogels to gradually release such substances over an extended period. For example, U.S. Patent No. 3,220,960 describes utilizing a hydrogel in the eye as a carrier for time release medicaments such as boric acid or penicillin. Similarly, U.S. Patent Nos. 3,551,556; 3,641,237; 4,003,991; and 4,271,143 disclose slowly releasing an active ingredient from an insoluble, cross-linked hydrogel in one form or another. Several compositions illustrated in the latter two patents are comprised of viscous, long-acting gel preparations where the prolongation of biological activity of the ophthalmic drug results from a slow erosion of the gel surface. The formulation in U.S. Patent No. 3,551,556 shows granular non-ionogenic, neutral, insoluble hydrogels which are useful for oral or intramuscular application. Further, many patents are directed to ocular insert devices which prolong the effect of a drug incorporated within the device. Such patents include U.S. Patent Nos. 3,811,444; 3,826,258; and 3,786,812.

These prior carriers of medicaments present certain difficulties during their use, particularly with ophthalmic drugs. The predominant complaint with long-acting gel formulations is blurred vision. Another difficulty is the inability to wear corrective contact lenses when a viscous material will be instilled and remain in the eye over an extended period of time. The ocular insert devices also present certain disadvantages with their use. When inserted into the conjunctival sac, such devices create a strong foreign body sensation and discomfort for the patient. The insert devices must be changed weekly. Additionally, the devices tend to fall out of the eye easily and cannot be used further by the patient since they are not capable of being sterilized.

Similarly, conventional contact lenses containing a sustained-release medicine carrier have drawbacks in practice. They have been found to obtain inadequately controlled or prolonged release characteristics making the conventional lenses unsuitable and impractical as sustained-release devices. The concept of soaking a high water content material in a drug solution has been used with conventional hydroxyethyl methacrylate based contact lenses, for example, a polymerized hydrophilic monomer or soft contact lens such as Soflens® manufactured by Bausch & Lomb. See Ruben et al, British J. Ophthal., 59:455 (1975). In practice, Soflens®, however, provides an inefficient system and is an unsuitable device for prolonged release. Experimental studies have shown that Soflens® will release 100% of pilocarpine hydrochloride in buffered saline and distilled water in merely 1½ and 2½ hours, respectively.

A commercially available sustained release ophthalmic device for the administration of pilocarpine, sold under the trade mark "Ocusert", comprises a central reservoir of the drug enclosed by a membrane through which the drug diffuses at a controlled rate. The device is typically of an ovoid shape with a major diameter of about 13.4 mm and a minor diameter of about 5.7 mm. The device cannot be used to correct vision of the patient.

The present invention seeks to provide an improved sustained release dosage form useful for topical, systemic or transdermal administration of a medicinal agent.

More particularly, the present invention provides a sustained-release polymeric hydrogel dosage form useful for topical, systemic or transdermal administration of a medicinal agent comprising a cross-linked hydrophilic polymer containing units derived from an amino acid monomer, and said medicinal agent in a therapeutically effective amount releasably bound to amino acid groups of said polymer.

The present sustained-release polymeric hydrogel dosage form does not undergo decomposition or deterioration in body fluids and is nontoxic therein. The polymeric matrix from which the device is formed is moldable to any desired shape, with moldability to the shape of the cornea of the eye being of major interest. In this latter connection a particular embodiment of this invention is an ophthalmic dosage form that can concurrently correct vision and release medication to the eye, i.e., a contact lens with both cosmetic and therapeutic value.

Hereafter, reference will be made to the accompanying drawings, in which:

FIG. 1 shows the release characteristics of a high water spin polymeric hydrogel with pilocarpine hydrochloride prepared in Example 5 in distilled water;

FIG. 2 shows the release characteristics of Ocusert-20® (an ophthalmic sustained-release device using an ethylenevinyl ac tate copolym r as the rat controlling membrane with pilocarpine, available from Alza Corp., Pal Alto, California) in distilled wat r;

FIG. 3 shows th r l as characteristics of Ocusert-40 (an ophthalmic sustained-rel as device using an ethylenevinyl ac tate copolym r as the rate controlling membran with pilocarpin , available from

Alza Corp., Palo Alto, California) in distill d water;

FIG. 4 shows the rel ase characteristics of Permalens® (an ext nded wear contact lens comprising a copolym r of hydroxy thyl methacrylate, vinyl pyrrolidon and methacrylic acid, availabl from Cooper Vision Incorp., Mountain View, California) with pilocarpine hydrochloride in distilled water;

FIG. 5 shows the release characteristics of a high water spin polymeric hydrogel with pilocarpine hydrochloride prepared in Example 6 in distilled water;

FIG. 6 shows the release characteristics of a high water spin polymeric hydrogel with pilocarpine hydrochloride prepared in Example 6 in buffered saline;

FIG. 7 shows the release characteristics of a triple spun high water spin polymeric hydrogel comprising polymer plus pilocarpine hydrochloride in middle layer prepared in Example 7 in distilled water;

FIG. 8 shows a cumulative percent release comparison of Permalens® and the high water spin polymeric hydrogel prepared in Example 5 in distilled water;

FIG. 9 shows a comparison of the release characteristics for the high water spin polymeric hydrogel prepared in Example 5, Permalens® with pilocarpine hydrochloride, Ocusert-20® and Ocusert-40® in distilled water;

FIG. 10 shows the same comparison as FIG. 9 on an expanded scale;

FIG. 11 shows a comparison of the release characteristics for the high water spin polymeric hydrogel prepared in Example 6 in distilled water and buffered saline;

FIG. 12 shows the same comparison as FIG. 11 on an expanded scale; and

FIG. 13 shows a comparison of the release characteristics for Ocusert-20® and Ocusert-40®.

As mentioned above, the sustained-release dosage form of this invention comprises a cross-linked hydrophilic polymer containing units derived from an amino acid monomer, and it contains a medicinal agent for the controlled-release administration to mammals of the desired active ingredient from the polymeric matrix and which is releasably bound to amino acid groups of the polymer.

The hydrophilic monomer used to prepare the polymers employed in this invention can be present in varying amounts, but desirably 50% to 90% w/w and, more preferably, 83% to 84% w/w of the total monomers present in the polymerization mixture. These monomers have an olefinic bond. They include, for example, the hydroxyalkyl esters and amides, both N-substituted and unsubstituted, of alpha-, beta-unsaturated carboxylic acids, N-vinyl lactams and 2-acrylamido-2-methylpropane sulfonic acid. Examples of alpha-, beta-unsaturated acids useful in this invention are acrylic acid, crotonic acid, methacrylic acid, itaconic acid, maleic acid, maleic anhydride and fumaric acid. The poly-functional alcohols which form the hydroxyalkyl esters include glycol, glycerol, propylene glycol, trimethylene glycol and other polyhydric alkanols, dialkylene glycols of 2 to 12 carbon atoms and polyalkylene glycols. Polyalkylene glycols are exemplified by triethylene glycol, tetraethylene glycol, pentaethylene glycol and hexaethylene glycol. The preferred hydrophilic monomers are the hydroxylalkyl esters, specifically hydroxyethyl methacrylate (HEMA).

Useful amides of the foregoing acids include diacetone acrylamide and N-mono-substituted diacetone acrylamide. Also useful are the amines of the foregoing acids such as mono- or di-alkylamino substituents.

A nitrogen containing monomer which may be used in the preparation of the polymers employed in this invention is conveniently referred to as N-vinyl lactam, which term includes (a) N-vinyl lactams per se and (b) other heterocyclic N-vinyl monomers. Illustrative of the N-vinyl lactams that can be employed in this invention are N-vinyl-2-pyrrolidinone, N-(1-methyl vinyl) pyrrolidone, N-vinyl-2-piperidone and N-vinyl-2-caprolactam which may be substituted in the lactam ring by one or more lower alkyl groups such as methyl, ethyl or propyl, e.g., N-vinyl-5-methyl pyrrolidinone, N-vinyl-3,3-dimethyl pyrrolidinone, N-vinyl-5-ethyl pyrrolidinone and N-vinyl-6-methyl piperidone. Illustrative of the other heterocyclic N-vinyl monomers which can be used in preparing the polymers of this invention are N-vinyl imidazole, N-vinyl succinimide, N-vinyl diglycolylimide, N-vinyl glutarimide, N-vinyl-3-morpholinone and N-vinyl-5-methyl-3-morpholinone. The lactams may be effectively employed alone or in admixture with other lactam monomers to give hydrogels having the foregoing desirable characteristics.

The second monomeric component of the polymer employed in this invention is an alpha-, beta-unsaturated carbonyl modified or unmodified amino acid monomer or monomers. This component can be present in varying amounts, desirably in an amount from 5% to 27 % w/w and, more preferably, about 6 % w/w of the total monomers present in the polymerization mixture. The modified or unmodified amino acid monomers ar hydrophilic compounds which contribute significantly to th swelling of th polymer in water and permit high r oxyg n diffusion.

The alpha-, beta-unsaturated carbonyl modifi r for the modified amino acids of this invention may be, for example, acrylic acid, crotonic acid, methacrylic acid, maleic acid, fumaric acid, itaconic acid and their functional d rivatives, i. ., acid chlorides, anhydrides, amides and esters. Th more preferred modifiers ar

methacrylic acid and methacroyl chloride.

An amino acid is an organic acid whos molecule contains both a carboxyl group (COOH) and an amino group (NH_2) coupled with an alkyl, cycloalkyl, aryl or h terocyclic structure, the alkyl, cycloalkyl or heterocyclic structure being free of olefinic unsaturation. The alpha-, beta-carbonyl substituent can be attached to either the amino group or the hydroxy group of the amino acid, depending on the structure of the amino acid. Additionally, the carbonyl substituent can attach to other reactive groups, if present, in the amino acid, e.g., thiol (SH) or phenolic hydroxyl.

Amino acids useful in the preparation of the modified acids of this invention include beta-alanine, gamma-aminobutyric acid, omega-aminocaproic acid, omega-aminododecanoic acid, beta-cycanoalanine, epsilon-methylhistidine, canavanine, djenkolic acid, 1-azaserine, gamma-methylene glutamic acid, N-methyl-tyrosine, glycine, alanine, serine, cystine, cysteine, lanthionine, phenylalanine, tyrosine, diiodotyrosine, tryptophan, histidine, aminobutyric acid, methionine, valine, norvaline, leucine, isoleucine, norleucine, arginine, ornithine, lysine, aspartic acid, glutamic acid, threonine, hydroxyglutamic acid, proline, hydroxyproline, asparagine, glutamine, desmosine, isodesmosine and 5-hydroxylysine. Preferred amino acids are glycine, glutamic acid, desmosine and isodesmosine.

It should be understood that other, though perhaps less common, amino acids occurring in nature or prepared synthetically, including those shown in the examples which follow, are within the scope of this invention. Reactive sites on the amino acids can be partially blocked by saturated nonpolymerizable substituents provided that one reactive site is substituted by the alpha-, beta-carbonyl substituent.

The polymers used in this invention can be cross-linked by all types of cross-linking compounds used in the prior art, see for instance, U.S. Patent Nos. 3,822,089; 4,152,508; and 4,440,919. The cross-linking agent can be employed in varying amounts and desirably in an amount from 0.1 % to 20 % w/w, preferably 0.5 % w/w, of the total monomers present. Examples of cross-linking agents include polyfunctional derivatives of the previously enumerated alpha-, beta-unsaturated acids, e.g., acrylic acid, methacrylic acid, crotonic acid, itaconic acid, maleic acid, fumaric acid, acrylamide, methacrylamide, and multi-vinyl substituted benzenes. More particularly these cross-linking agents include the following: ethylene glycol diacrylate or dimethacrylate, diethylene glycol diacrylate or dimethacrylate, triethylene glycol diacrylate or dimethacrylate, tetraethylene glycol diacrylate or dimethacrylate, polyethylene glycol diacrylate or dimethacrylate, trimethylolpropane triacrylate or trimethacrylate, bisphenol A diacrylate or dimethacrylate, ethoxylated bisphenol A diacrylate or dimethacrylate, pentaerythritol tri- and tetra-acrylate or methacrylate, tetramethylene diacrylate or dimethacrylate, methylene bisacrylamide or methacrylamide, dimethylene bisacrylamide or methacrylamide, N,N'-dihydroxyethylene bisacrylamide or methacrylamide, hexamethylene bisacrylamide or methacrylamide, decamethylene bisacrylamide or methacrylamide, divinyl benzene, vinyl methacrylate, and allyl methacrylate.

Still other useful cross-linking agents include 1,3-bis (4-methacryloyl oxyalkyl) tetra disiloxane and similar poly (organo-siloxane) monomers set forth in U.S. Patent No. 4,153,641. Another group of useful cross-linking agents are the resonance free di(alkylene tertiary amine) cyclic compounds, e.g., N,N'-divinyl ethylene urea, as disclosed in U.S. Patent No. 4,436,887. Yet another group are di- or polyvinyl ethers of di- or polyvalent alcohols such as ethylene glycol divinyl ether.

For some applications the polymerizates formed from the above hydrophilic monomer(s), modified or unmodified amino acid monomer(s) and cross-linking agent(s) may lack the desired physical handling properties. It is another aspect of this invention in such circumstances to incorporate one or more hydrophobic monomers in the above polymers in varying amounts, desirably from 8 % to 20 % w/w of the total monomers present. More preferably the hydrophobic monomer would be present in an amount of 10 % w/w of the total monomers present. Among other things, the hydrophobic monomers are useful as modulus modifiers.

The modulus modifier may be, for example, cycloalkyl ester, tertiary-butyl styrene and polycyclic acrylate or methacrylate, as well as mixtures thereof. More particularly the polycyclic modifiers may be isobornyl acrylate, isobornyl methacrylate, dicyclopentanedienyl acrylate, dicyclopentanedienyl methacrylate, adamantyl acrylate, adamantyl methacrylate, isopinocamphyl acrylate and isopinocamphyl methacrylate, and mixtures thereof. The cycloalkyl ester modifier is of formula I below. Illustrative of these cycloalkyl modifiers are menthyl methacrylate, menthyl acrylate, tertiary-butyl cyclohexyl methacrylate, isohexyl cyclopentyl acrylate, and methylisopentyl cyclooctyl acrylate.